## REMARKS

Claims 1, 26, 56-58 and 60-86 are pending. Claims 25, 27-55, 59, 67, 68, 71, 74, 80, and 82-84 have been cancelled without prejudice or disclaimer. Claims 1, 26, 57-58, 60-66, 69-70, 72-73 and 86 are amended herein. Upon entry of the present amendment, claims 1, 26, 56-58, 60-66, 69, 70, 72, 73, 75-79, 81, and 86 will be pending.

**Support for the Amendments**

Support for the amendments to claims 1, 26, 56, 57-58, 60-66, 69-70, 72-73, 75-79, 81, and 86 can be found throughout the instant specification as filed. For example, claim 1 as amended recites, "A method of inhibiting the GTPase activity of dynamin in a cell or synaptosome," support for which is found throughout the specification, such as at page 4, lines 6 – 9, which states the invention in one or more embodiments relates to compounds capable of inhibiting the GTPase activity of dynamin; and at page 6, lines 23 – 27; page 24, lines 9 – 33, which describes the preparation of isolated nerve terminals (synaptosomes); and for instance, at page 30, lines 1 – 10, which teaches that inhibition of the GTPase activity of dynamins I and II blocks both synaptic vesicle endocytosis (SVE) in synaptosomes and receptor mediated endocytosis (RME). Further, claim 1 has been amended to define the spacer (Sp) group of a compound of Formula I as "consisting of a 1 to 7 atom chain." Linker group (W) is also now defined as comprising "CH or a linker group of up to 3 atoms in length." Support for these amendments is found in the specification at least at page 15, lines 1 – 4 and page 15, lines 20 – 24.

Claim 1 is also amended to define the Z group as "a carbocyclic or heterocyclic group, consisting of one ring independently having 5 or 6 ring members and at least two substituents independently selected from nitro, NH, amino, cyano, halo, hydroxy, carboxy, oxo, sulfur, sulfhydryl, $C_1$-$C_2$ alkoxy, $C_1$-$C_2$ acyl, or a $C_1$-$C_2$ alkyl or $C_1$-$C_2$ alkenyl group with at least one substituent selected from nitro, NH, amino, cyano, halo, hydroxy, carboxy, oxo, sulfur, sulfhydryl, $C_1$-$C_2$ alkoxy and $C_1$-$C_2$ acyl." Support for the Z group being a heterocyclic group is found in claim 1 as filed (see option (c)). Moreover, support for the Z group being substituted with a $C_1 - C_2$ alkoxy is provided by original claim 58 options (ii) and (iii), showing that the omission from claim 1 of the Z group having a $C_1 - C_2$ alkoxy was a typographical error.

Claim 26 as amended recites, "The method of claim 1, wherein said contacting of a cell or synaptosome consists of contacting of a cell with an effective amount of a compound of formula I, or a physiologically acceptable salt thereof, to inhibit dynamin-dependent endocytosis in said cell." Support for claim 26 as presently amended is clearly found in the specification as filed at least at page 4, lines 6 – 14.

Claim 57 as amended recites, "Y is cyano, nitro, amino, carboxy, hydroxy, sulfhydryl, or thiocarboxy; or W, V and Y form a 5 or 6 membered substituted or unsubstituted heterocyclic or carboxylic ring fused with Z, wherein the heterocyclic ring includes from 1 to 3 heteroatoms selected from O, N and S, and the carbocyclic or heterocyclic ring, when substituted, has at least one substituent selected from cyano, nitro, amino, hydroxy, sulfhydryl, carboxy and thiocarboxy, or a $C_1$-$C_2$ group substituted with a group selected from cyano, nitro, amino, hydroxy, sulfhydryl, carboxy and thiocarboxy; and R is CXR'." Support for this amendment is provided at least by claim 1 as originally filed.

Claim 60 as amended recites, "the Z group is an aryl group with two of said substituents in ortho positions relative to one another." Support for this amendment is provided by at least original claims 10 to 12 as filed.

Claim 63 as amended recites, "Y is cyano, nitro, amino, carboxy, hydroxy, sulfhydryl or thiocarboxy." Support for this amendment is provided at least by claim 1 as originally filed.

Claim 64 as amended recites, "the Z group is an aryl group with at least two substituents in ortho positions relative to one another, wherein said substituents are independently selected from nitro, NH, amino, cyano, hydroxy, carboxy, oxo and sulphur." Claims 65 and 66 are similarly amended. Support for these amendments is found in the specification as filed at least at page 15, lines 2 – 3; page 39, Table 1 and lines 5 – 11; and in original claim 17 as filed.

The amendments to claim 69 correlate with those made to claim 1.

Claim 70 as amended recites, "$R_2$ to $R_4$ are other than hydrogen." Support for this amendment is provided at least by the exemplified compounds in Table 1 at page 39 of the specification as filed and, for instance, by original claim 73 as filed.

Claim 86 as amended recites, "A method for preventing or treating epilepsy or inhibiting dynamin-dependent endocytosis in a mammal, the method comprising administering to a mammal an effective amount of the compound of formula I, or a physiologically acceptable salt or prodrug thereof to prevent or treat epilepsy or inhibit dynamin-dependent endocytosis in said

mammal . . ." Support for claim 86 as amended can be found in the specification as filed at least as described above in connection with amended claim 26 and, for example, at page 18, lines 15 – 18 and line 29 of the specification as filed, which specifically identify epilepsy.

No new matter has been added by way of these amendments. The amendments to the claims should in no way be construed as acquiescence to any of the Examiner's rejections and were made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

***Rejection of Claims 1, 26, 56-58 and 60-86 Under 35 U.S.C. §112, First Paragraph***

The Office Action rejects claims 1, 26, 56-58, and 60-86 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with both the written description and enablement requirements. For the reasons detailed below, Applicants respectfully disagree and traverse the rejections.

**"New Matter" Rejection**

The Office Action alleges in reference to independent claim 1 and claims 26, 56-58, and 60-86 depending therefrom that "[i]t is not dynamin that is being "contacted," but rather cells CONTAINING dynamin. Therefore this phrase constitutes new matter." (Office action mailed May 29, 2008, page 3, third paragraph). Applicants respectfully disagree and traverse this rejection. However, without in any way acquiescing to the rejections/objections and in order to expedite prosecution of the application, claim 1 has been amended to recite, "***contacting a cell or synaptosome*** with an effective amount of a compound of formula I, or a physiologically acceptable salt thereof, to inhibit said GTPase activity in said cell or synaptosome," thereby obviating the rejection.

The Office Action also alleges that

> [c]laims 82 and 84 also contain new matter. Claim 82 contains the phrases "diseases or conditions associated with cell vesicle trafficking" and "diseases or conditions characterized by synaptic signal transmission." Claim 84 contains the phrase "disease or condition is associated with cell vesicle trafficking or is characterized by synaptic signal transmission." Applicant states that support for these phrases can be found at pg. 16, line 28 to page 17, line 2, and pg. 17, line 16-22. However, these sections of the specification do not support these phrases.

> Therefore, these phrases constitute new matter. (Office action mailed May 29, 2008, page 3, last paragraph, to page 4).

Applicants traverse this rejection. However, solely in the interest of expediting prosecution of the instant invention, claims 82 and 84 have been cancelled herein without prejudice, rendering the rejection moot.

> The Office Action further alleges,
>
> Claim 61 also contain [*sic*] new matter. Claim contains the phrase "side ring." There is no support for "side ring" in the specification in regard to group Z. Therefore, these phrases constitute new matter. (Office action mailed May 29, 2008, page 4, first paragraph).

Applicants traverse this rejection. However, solely in the interest of expediting prosecution of the instant invention, claim 61 is amended herein to omit the phrase "side ring," thereby rendering the rejection of claim 61 moot.

**Written Description Rejection**

The Office rejects claim 26 and 86 as allegedly lacking an adequate written description for reciting the term "prodrug." Specifically, the Office Action alleges,

> The present disclosure fails to recite a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation of "prodrug" such that the artisan would readily identify the scope of this active agent. Because there is no support for "prodrug" in the specification, it is not clear that applicant had possession of the claimed invention at the time of filing. (Office action mailed May 29, 2008, page 6, first paragraph).

For the reasons detailed below, Applicants respectfully disagree and traverse this rejection.

Nevertheless, claim 26 has been amended to delete the term "prodrug," thereby rendering the rejection moot.

An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the invention had possession of the claimed invention (M.P.E.P. 2163.04 II.A.3(a)).

The term "prodrug" was well known in the art at the time of filing and the scope of the term would be well understood by one of ordinary skill in the art as evidenced in Exhibit A, which defines the term prodrug as "A class of drugs, initially in inactive form, that are converted

into active form in the body by normal metabolic processes." (The American Heritage® Stedman's Medical Dictionary. Houghton Mifflin Company. Copyright 2002, 2001, 1995 by Houghton Mifflin Company, published by <Dictionary.com http://dictionary.reference.com/browse/prodrug>)

Moreover, the specification not only clearly exemplifies a range of prodrug forms, but also provides specific exemplification of the provision of such prodrugs to the skilled artisan, as well as their utility. More particularly, Applicants draw the Examiner's attention to page 16, lines 13-27 of the specification as filed, which exemplifies the range of possible prodrugs useful in the instant invention, including, for instance, amides and alkyl esters that are covalently linked to free amino, amido, hydroxyl or carboxylic groups. As stated in this section of the instant specification, "A prodrug may for example be inactive when administered but undergo *in vivo* modification into the active compound that binds to dynamin such that the GTPase activity of the protein is inhibited, as a result of cleavage or hydrolysis of bonds or other form of bond modification post administration. Preferably, the prodrug form of the active compound will have greater cell membrane permeability than the active compound thereby enhancing potency of the active compound." (page 16, lines 19-24). Moreover, as also stated, "A prodrug may also be designed to minimize premature *in vivo* hydrolysis of the prodrug external of the cell such that the cell membrane permeability characteristics of the prodrug are maintained for optimum availability to cells and for systemic use of the compound" (page 16, lines 25-27).

Further support for prodrugs is provided in the specification as filed by Example 3 at page 43, line 22 to page 47, line 13. In particular, the instant specification as filed, at page 43, line 23 to page 44, line 3, and at Scheme 5 at page 44, describes a reaction for providing esterified forms of compounds of Formula I. Moreover, Tables 2 and 3 at pages 45 and 46 of the instant specification as filed exemplify various prodrug forms of bis-tyrphostin Bis-T(1). As also stated at page 47, lines 1-13, the esterified prodrug identified as Pro-BisT (see Table 3, page 46) was shown to be converted into the active compound bis-tyrphostin within cells, inhibit receptor mediated endocytosis (RME) of transferrin or EGF in the cell lines HeLa, HER14, COS7, Swiss 3T3, A431, B104 and B35, and was found to be significantly more potent than Bis-T (~ 30x) indicating greatly improved ability to penetrate cells compared to bis-tyrphostin. The specification as filed further states that prodrug 80-1 (see Table 3) was found to inhibit

RME at similar concentrations to Pro-BisT and was developed to reduce premature hydrolysis of the prodrug in the external cellular environment prior to passage into cells.

In view of the above-referenced disclosure, and further in view of the art-recognized meaning of the term "prodrug" at the time of filing, one of ordinary skill in the art would have recognized Applicants' possession of the claimed invention at the time of filing. This is all that is required to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Accordingly, this basis for the rejection of claim 86 should be withdrawn.

**Enablement Rejection**

The Office Action rejects claims 1, 26, 56-58, and 60-86 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Office Action alleges that "the specification does not reasonably provide enablement for prophylaxis or treatment of disease mediated by dynamin-dependent endocytosis." (Office action mailed May 29, 2008, page 6, second paragraph). For the reasons set forth below, Applicants respectfully disagree and traverse this rejection.

The standard for enablement set forth in 35 U.S.C. 112, first paragraph, requires that Applicants provide a description of the invention sufficient "to enable any person skilled in the art to which it pertains . . .to make and use" the invention. The proper test of enablement is set forth in *United States v. Telectronics, Inc.*, (857 F.2d 778, 785, 8 USPQ2d at 1217, 1223 (Fed. Cir. 1988)):

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation.

Applicants' specification should not be read in isolation; rather, Applicants' specification must be read in light of the knowledge present in the art at the time of filing. "A patent need not teach, and preferably omits, what is well known in the art." M.P.E.P. 2164.01 Thus, compliance with the enablement standard does not require that Applicants describe methods known to the skilled artisan. As detailed below, the specification as filed clearly provides ample disclosure to allow one of ordinary skill in the art to make and use the claimed invention absent undue experimentation. Applicants consider the individual components of the enablement rejection below.

*1. Prophylaxis of disease*

The Office asserts that the treatment of epilepsy is unpredictable. In support of this assertion, the Office cites Duncan et al (Lancet 367: 1087-1100, 2006), which allegedly teaches that conventional methods for treating epilepsy are effective in the majority of individuals. Claim 1 is now directed to methods for inhibiting the GTPase activity of dynamin in a cell or synaptosome.

The specification as filed presents working examples of methods for inhibiting the GTPase activity of dynamin in a cell or synaptosome. Specifically, Applicants invite the Examiner's attention to Example 1 of the specification as filed (page 22, line 3 to page 30, line 10 of the instant specification as filed), which discloses that bis-tyrphostin inhibited the GTPase activity of both dynamin I and dynamin II (see page 26, lines 10-27 of the specification as filed). Indeed, the specification as filed discloses bis-tyrphostin as an effective inhibitor of both dynamin I-mediated synaptic vesicle retrieval in synaptosomes (see page 28, line 9 to page 29, line 2 of the instant specification as filed) and dynamin II-mediated receptor-mediated endocytosis of transferrin in Swiss 3T3 and HER14 cells (see page 29, lines 3-13 of the instant specification as filed). Thus, Applicants respectfully submit that the specification fully enables a method for inhibiting the GTPase activity of dynamin in a cell or synaptosome, as is recited in claim 1 as presently amended.

Regarding claim 86, which is directed to methods for "preventing or treating epilepsy or inhibiting dynamin-dependent endocytosis in a mammal," the specification also provides ample disclosure for one of ordinary skill in the art to practice such a method without undue experimentation. "The test [of enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance." *Ex parte Forman*, 230 USPQ 546, 547 (Bd. App. 1986). As also pointed out by the Federal Circuit in *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ 2d 1321 (1990), "[i]t is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification." 15 USPQ 2d at 1329. See, also *In re Brana*, 34 USPQ 2d 1436 (Fed. Cir. 1995). Here, Applicants submit that the instant specification explicitly discloses, "The inhibition of dynamin-dependent endocytosis of cells is applicable to the treatment of epilepsy and neurological disorders and conditions" (see abstract of the instant

specification as filed). Further, at least at page 20, line 4 to page 22, line 2 of the instant specification as filed, specific instruction is provided regarding the formulation of pharmaceutical compositions of the instant invention for *in vivo* administration, including direct instruction regarding preferred routes of administration for delivery of such formulations to a mammal. Accordingly, at least in view of the extensive disclosure found in the instant specification as filed regarding use of the compounds of the instant invention to prevent or treat epilepsy and/or inhibit dynamin-dependent endocytosis, which further includes *in vivo* formulation, dosage and route of administration guidance, Applicants respectfully submit that the specification as filed amply enables one of ordinary skill in the art to make and use the instant invention as claimed absent undue experimentation. Accordingly, this basis for the rejection should be withdrawn.

*2. Scope of the diseases being treated*

In support of the enablement rejection, the Examiner asserts that Applicants have failed to enable all of the diseases related to dynamin-dependent endocytosis. Applicants respectfully disagree. Nevertheless, Applicants claims are now directed to methods for inhibiting the GTPase activity of dynamin in a cell or synaptosome (claim 1) and to methods for treating or preventing epilepsy (claim 86).

As detailed above, Applicants specification clearly enables methods for inhibiting GTPase activity in a cell or synaptosome. In particular, Applicants teach that the present invention is useful for the prophylaxis or treatment of conditions that involve dynamin-dependent endocytosis or the inhibition of dynamin-dependent endocytosis (page 16, line 31, to page 17, line 2). Such conditions include epilepsy as indicated at page 18, lines 15-18, and as recited in claim 86. Accordingly, this basis for the rejection should be withdrawn.

*3. Scope of active agents*

In further support of the enablement rejection, the Office alleges that Applicants have not enabled compounds of formula I because such compounds include "a plethora of functional groups including a vast range of heteros" and the amount of screening required to identify those compounds that work would be undue. Applicants respectfully disagree.

The Office appears to suggest that it is the number of compounds to be screened that is determinative of undue experimentation. This is not the legal standard for enablement, however.

The fact that some experimentation may be required to practice the invention does not indicate that the claims lack enablement so long as the experimentation is merely routine. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In Wands, the claims at issue were directed to immunoassays that required the use of monoclonal antibodies. The identification of these antibodies required extensive screening, and the court considered the question of whether undue experimentation would be required to carry out the screens. The court found that the specification enabled the claims because "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." Id. at 740, 8 USPQ2d at 1406. The Wands court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." Id., 8 USPQ2d at 1407.

The present case is analogous to Wands in all important respects because although some screening might be required to identify those compounds that work in the claimed methods, no more than routine experimentation would be required to identify such compounds. Independent claim 1, from which claims 26, 56-58, 60-66, 69-70, 72-73, 75-79, 81, and 86 depend, defines compounds of Formula I as having a spacer (Sp) consisting of a 1 to 7 atom chain. The linker group (W) is defined as being CH or a group of up to 3 atoms in length. Further, claims 1 and 86 now define the Z group as comprising a carbocyclic or heterocyclic group, consisting of one ring independently having five or six ring members and at least two substituents selected from those recited in the claim.

As supported by the instant specification at page 39, lines 3 – 14, compounds of Formula I with a spacer (Sp) of up to at least 7 atoms in length were found to retain dynamin GTPase inhibitory activity. The same methods could readily be used to identify virtually any compound that inhibits dynamin GTPase activity. Furthermore, synthetic schemes for the synthesis of compounds of Formula I are set out in the specification as filed, at least at page 30, line 24 to page 31, line 10 and page 40, lines 3 to page 43, line 21. Indeed, methods for the synthesis of specific compounds are set out at pages 32 to 38. Although the compounds specifically exemplified in the body of the specification show the Z group as being phenyl, a person of ordinary skill in the art can readily provide corresponding compounds as now claimed, in which the phenyl is substituted for a heterocyclic group. Moreover, based on the teachings provided in the instant specification as filed – in particular, the exemplification of a range of active

compounds in Table 1 at page 39, together with the associated discussion relating to those compounds and the development of analogues of bis-tyrphostin (Bis-T) – it is submitted that the instant specification provides ample guidance to practice the invention as claimed without undue experimentation.

In further support of the enablement rejection, the Office alleges that it is unpredictable how compounds of Formula I can inhibit any dynamin activity other than GTPase activity. This basis for the rejection is obviated by the present amendment.

In sum, Applicants' specification and the extensive knowledge of one of ordinary skill in the art would clearly enable one of ordinary skill in the art to make and use the claimed methods without undue experimentation. Accordingly, Applicants request reconsideration and withdrawal of the rejection of claims 1, 26, 56-58, and 60-86 under 35 U.S.C. §112, first paragraph.

***Rejection of Claims 26, 56-58, 60-78 and 80-85 Under 35 U.S.C. §112, Second Paragraph***

The Office Action rejects claims 26, 56-58, 60-78 and 80-85 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants traverse this rejection.

Specifically, the Office alleges that "the term 'mediated' [in claim 26] is a 'term of degree' which is inadequately defined." In addition, the Office alleges that the phrase "side ring" in claim 61 "is indefinite since its modifying function is unclear." Applicants respectfully disagree and traverse the rejection. However, without in any way acquiescing to the rejections/objections and in order to expedite prosecution of the application, the claims have been amended as set forth above, thereby obviating the rejection of claims 26, 56-58, 60-78 and 80-85 under 35 U.S.C. §112, second paragraph.

***Rejection of Claims 1, 79 and 86 Under 35 U.S.C. §102(b)***

Claims 1, 79 and 86 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Gazit *et al.* (Journal of Medicinal Chemistry 1996; hereinafter "Gazit"). Applicants respectfully disagree with the rejection, and request that it be withdrawn.

To support an anticipation rejection the prior art reference must disclose each and every element present in the claimed invention. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegall Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631. In the present case, Gazit fails to describe all of the elements present in the claimed invention, and thus cannot serve as an anticipation.

Gazit describes inhibitors of platelet-derived growth factor tyrosine kinase activity. In particular, Gazit describes assays for receptor autophosphorylation in Swiss 3T3 cells in culture. Gazit fails to describe any method of inhibiting the GTPase activity of dynamin by contacting a cell with an effective amount of a compound of formula 1 as recited by independent claim 1, from which claim 79 depends, nor does Gazit describe any method for preventing or treating epilepsy or inhibiting dynamin-dependent endocytosis in a mammal by administering an effective amount of a compound of formula 1, as recited by claim 86. In fact, Gazit is entirely silent with regard to dynamin. Thus, Gazit fails to anticipate Applicants invention as presently claimed.

In support of the anticipation rejection, the Examiner alleges that "When bis-T23 is administered, it will inherently inhibit dynamin 'activity'." Applicants respectfully disagree. M.P.E.P. §2112 (IV) directs that the Examiner must provide rationale or evidence tending to show inherency:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)...In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). 'To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill'...In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)...In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic **necessarily** flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). [Emphasis added.]

The Doctrine of Inherency indicates that the claimed property or therapeutic effect must be the **necessary** consequence of the prior art disclosure. In other words, every time one conducts the prior art process, the claimed property or therapeutic effect **must** occur. If one conducts the prior art method and does not get the claimed property or therapeutic effect, then the claimed process is not inherent in the prior art.

There is nothing in Gazit that would lead one to conclude that the amount of any compound used was sufficient to inhibit dynamin GTPase activity as recited in claims 1 and 76 or to inhibit dynamin-dependent endocytosis as recited in claim 86 in the treated Swiss 3T3 cells. To serve as an anticipation, it is not sufficient that the amount of the compound **might** have been sufficient to inhibit dynamin GTPase activity or dynamin-dependent endocytosis. To serve as an anticipation, the Examiner must provide evidence showing that the compound would necessarily have this effect. In the absence of facts and/or technical reasoning indicating that the compounds administered to the Swiss 3T3 cells would necessarily inhibit dynamin GTPase activity or dynamin-dependent endocytosis, the rejection is improper and should be withdrawn.

In sum, Gazit fails to describe any method for inhibiting the GTPase activity of dynamin or for inhibiting dynamin-dependent endocytosis. The Examiner has provided no evidence indicating that any of the compounds described by Gazit would inherently have these effects when administered to a Swiss 3T3 cell under the specific conditions described by Gazit. Accordingly, the rejection of claims 1, 79 and 86 under 35 U.S.C. § 102(b) should be withdrawn.

***Rejection of Claims 1, 26, 56-58, 60-79 and 80-86 Under 35 U.S.C. §103(a)***

The Office further rejects claims 1, 79 and 86 under 35 U.S.C. §103(a) as being obvious over Gazit *et al.* in view of Ahn *et al.*, (*Journal of Biological Chemistry* 1999). As detailed below, Applicants respectfully disagree and traverse the rejection.

To establish a *prima facie* case of obviousness, the Examiner must establish that the prior art included each element claimed (M.P.E.P. 2143). In addition, "[a] patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." *KSR International Co. v. Teleflex Inc.* 167 L. Ed. 2d 705, 712. The Supreme Court in *KSR* reaffirmed the familiar framework for determining obviousness as set forth in *Graham v. John Deere Co.* (383 U.S. 1, 148 USPQ 459 (1966)), but stated that the

Federal Circuit had erred by applying the teaching-suggestion-motivation (TSM) test in an overly rigid and formalistic way.

Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985). The combination of Gazit and Ahn fail to support the rejection of the claims as obvious because the references fail to describe each element of the claimed invention.

As set forth above, Gazit fails to describe methods of inhibiting the GTPase activity of dynamin as recited in claims 1 and 79. Gazit also fails to describe methods for preventing or treating epilepsy or inhibiting dynamin-dependent endocytosis in a mammal as recited in claim 86.

Ahn fails to remedy the deficiencies of Gazit. Ahn merely describes a study testing the hypothesis that tyrosine kinase activity **might** regulate endocytosis by acting on accessory molecules relevant to receptor internalization, such as dynamin. More particularly, Ahn reports that tyrosine phosphorylation of dynamin I by the tyrosine kinase c-Src is required for internalization of ß-2-adrenergic receptors (ß2-ARs) in Hek293 cells transfected with the dynamin protein. Transfected cells were used because dynamin I is not native to HEK293 cells, which normally express only dynamin II. Therefore, the cell model described by Ahn is artificial and does not necessarily reflect the biology of cells that endogenously express dynamin I.

Ahn identifies "[t]wo tyrosine residues, $Tyr^{231}$ and $Tyr^{597}$ [residing in the GTPase and pleckstrin homology (PH) domains of dynamin, respectively] as the major phosphorylation sites [of dynamin]. Mutation of these residues to phenylalanine dramatically decreases the c-Src-mediated phosphorylation of dynamin following $\beta_2$-AR stimulation" (*Ibid*). Ahn *et al.* concludes that "agonist-induced, c-Src-mediated tyrosine phosphorylation of dynamin is

essential for [dynamin's] function in clathrin mediated G protein-coupled receptor endocytosis" (*Ibid*). Ahn also states that "phosphorylation of $Tyr^{231}$ might regulate the GTPase activity of dynamin by controlling [. . .] intermolecular interactions" (*Id*, page 1188). Tellingly, however, Ahn *et al.* offers no evidence that the GTPase activity of dynamin was in any way affected by c-Src phosphorylation. Rather, Ahn simply discloses that the 2 Tyr residues are contained in two key functional dynamin domains, and that such residues are necessary for endocytosis of β2-AR. Moreover, Ahn provides no evidence that the Tyr mutations to phenylalanine were not themselves inhibitory to dynamin function, and that, as such, the cells had in fact been transfected with a dynamin form that was already dominant-negative. Hence, it cannot be concluded from Ahn that the reported dynamin tyrosine phosphorylation was the cause of $\beta_2$-AR endocytic failure.

The combination of Gazit and Ahn would also not have provoked the skilled artisan at the time of filing to contemplate the methods of the instant claims, especially in view of high profile references in the art at the time of filing that taught that dynamin-mediated endocytosis was not regulated by tyrosine phosphorylation of dynamin protein as evidenced in Tan *et al.* (*Nat. Cell Biol.*, 5(8): 701-710, submitted herewith as Appendix B). Applicants note that Phillip J. Robinson, who is a co-inventor of the present application, is a co-author of Tan *et al.* Tan *et al.* discloses that phosphorylation of dynamin I on serine residues Ser 774 and Ser 778 by cyclin-dependent kinase (Cdk5) is essential for synaptic vesicle endocytosis (SVE), and reports that Cdk5 thereby has an essential role in synaptic vesicle endocytosis (SVE).

Relevantly, Tan further states at page 701, left column, to right column, line 17, that SVE is required for maintaining the small pool of synaptic vesicles within nerve terminals after exocytosis and is activated by a calcineurin-mediated dephosphorylation event of serines, but not tyrosine amino acid residues. Tan *et al.* discloses that "[e]ight proteins, collectively called dephosphins [which include dynamin I] are dephosphorylated by calcinuerin in nerve terminals [. . . ] The dephosphins are constitutively phosphorylated in resting nerve terminals, and their rephosphorylation after termination of SVE is essential for subsequent rounds of endocytosis" (*Ibid*) . Tan notes the demonstration in the present study that Cdk5 is essential for SVE represents the first identified dephoshin kinase and further, rules out protein kinase C (PKC, a serine/threonine kinase) which had been postulated as the dephosphin kinase responsible for SVE.

In contrast to Tan *et al.*, Tomizawa *et al.* (*J. Cell Biol.* 163(4): 813-824, submitted herewith as Appendix C), teaches that Cdk5 phosphorylates Thr 780 and negatively regulates SVE. Tomizawa states that "only Thr 780 of dynamin I was phosphorylated by Cdk5" (Tomizawa *et al.*, page 816). In particular, Tomizawa *et al.* state that their results, "show for the first time that Cdk5-dependent phosphorylation of amphiphysin I has a critical role in the regulation of synaptic vesicle endocytosis" (Tomizawa *et al.*, page 821). Although the findings of Tomizawa *et al.* contradict those of Tan *et al.*, most relevant to consideration of the instant claims is the fact that both Tan et al. and Tomizawa et al. teach away from SVE/dynamin mediated endocytosis as being regulated by tyrosine phosphorylation of dynamin protein and thereby, from the use of inhibitors of protein tryrosine kinase as inhibitors of dynamin and endocytosis.

Moreover, given that Gazit *et al.* disclose use of dimeric tyrphostins solely in view of the *dimeric* nature of active EGFR (which uses ATP as a substrate for its kinase activity *as distinct from* GTP), one of ordinary skill in the art at the priority date would not have had reason to select a *dimeric* tyrphostin or other compound of formula I (given their dimeric nature) to inhibit GTPase activity of dynamin.

Further, even if one of ordinary skill in the art at the priority date had considered compounds for use in inhibition of the GTPase activity of dynamin as presently claimed (and there is no evidence or reason that the skilled artisan would have in view of the teachings of Tan *et al.* and Tomizawa *et al.*), Applicants submit that the skilled artisan would have considered small, monomeric compounds, rather than large dimeric tyrphostins due to the likely greater cell permeability (and thereby efficacy) of such small compounds.

In sum, Gazit and Ahn fail to teach or suggest methods of inhibiting the GTPase activity of dynamin with an effective amount of a compound of formula I as recited in claims 1 and 79, and further fail to teach or suggest methods for preventing or treating epilepsy or inhibiting dynamin-dependent endocytosis in a mammal by administering a compound of formula I as recited in claim 86.

The Office also rejects claims 26, 56-58, 60-78 and 80-85 under 35 U.S.C. §103(a) as obvious over Gazit in view of Jassar *et al.* (Brain Research 775"127-133, 1997; hereinafter "Jasser"). Applicants respectfully disagree and traverse this rejection. As an initial matter,

Applicants note that claims 67-68, 71, 74, 80 and 82-85 are cancelled thereby rendering the rejection moot as applied to these claims.

As acknowledged by the Examiner, Gazit does not teach a therapeutic treatment of epilepsy or any other disease by regulating dynamin-dependent endocytosis as recited by claims 26, 56-58, 60-66, 69-70, 72-73, 75-78 and 81. Jassar fails to remedy the deficiencies Gazit.

Jassar relates to a study purporting to show that phosphorylation is important for the activation and long term maintenance of GABA of $GABA_A$ receptors and that tyrosine kinase modulates GABA mediated neurotransmission. In particular, Jassar states that his "results suggest that genistein and tyrphostin, through their actions on PTK, attenuate the muscimol-evoked chloride currents and provide evidence for the modulation of $GABA_A$ receptor function by PTK" (Jassar *et al.*, page 132). Jassar *et al.* specifically state "that inhibition of PTK by genistein and tyrphostin B-44(-) results in a significant blockade of the response to muscimol and is consistent with modulation of $GABA_A$ receptor by PTK phosphorylation" (*Ibid*, page 130). In support of the rejection, the Office alleges that "[i]t would have been obvious to a person having ordinary skill in the art to use the compound of Gazit in a method for treating epilepsy, since GABA neurotransmission is aberrant in epilepsy and GABA neurtransmission [*sic*] can be attenuated by inhibition of PTK." (Office action mailed May 29, 2008, page 16, first paragraph). Applicants respectfully disagree.

First, the Jassar reference fails to examine epilepsy, dynamin or endocytosis. At best, Jassar merely speculates that "a better understanding of the cellular mechanisms underlying the actions of a ubiquitous central inhibitory transmitter may have important therapeutic implications in conditions such as epilepsy where GABA neurotransmission is aberrant" (see page 133, Col. 1, lines 9-13). Second, the studies described by Jassar did not employ a dimeric tyrphostin (or compound of formula I as now claimed). Rather, the B44(-) tyrphostin described by Jassar is a monomeric compound which was developed as a benzene substituted monomeric tyrphostin analogue (*see* Gazit *et al.* Tyrphostins. 2. Heterocyclic and alpha-substituted benzylidenemalononitrile tyrphostins as potent inhibitors of EGF receptor and ErbB2/neu tyrosine kinases. *J.Med.Chem.* 34 (6):1996-1907, 1991; this article was previously submitted to the USPTO by way of an Information Disclosure Statement).

More particularly, Jassar merely suggests phosphorylation mechanisms in the maintenance of $GABA_A$ and that protein tyrosine kinase (PTK) phosphorylation might modulate

GABA-mediated neurotransmission in the forebrain. Jassar fails to teach or suggest a role for dynamin or endocytosis, nor does it disclose, suggest or provide any motivation to employ dimeric tyrphostins (or compounds of Formula I as now claimed) to inhibit the GTPase activity of dynamin, whether taken alone or in combination with Gazit. Indeed, as discussed above, a person of ordinary skill in the art at the priority date would have been led away from the invention as now claimed, given that Gazit simply disclosed the use of dimeric tyrphostins to inhibit the tyrosine kinase activity of the dimeric active form of EGFR, whereas Tan *et al.* and Tomizawa et al. taught away from SVE/dynamin mediated endocytosis as being regulated by tyrosine phosphorylation of dynamin protein and thereby, from the use of inhibitors of protein tryrosine kinase as inhibitors of dynamin and endocytosis.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 26, 56-58, 60-79 and 80-86 under 35 U.S.C. §103(a).

## SUMMARY

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: December 1, 2008

Respectfully submitted,

By /Christopher R. Cowles/
Christopher R. Cowles
Registration No.: 59,931
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 239-0483
Attorneys/Agents For Applicant